A Model Analysis of Arterial Oxygen Desaturation during Apnea in Preterm Infants

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Abstract

Rapid arterial O_2 desaturation during apnea in the preterm infant has obvious clinical implications but to date no adequate explanation for why it exists. Understanding the factors influencing the rate of arterial O_2 desaturation during apnea ($\dot{S}a_{O_2}$) is complicated by the non-linear O_2 dissociation curve, falling pulmonary O_2 uptake, and by the fact that O_2 desaturation is biphasic, exhibiting a rapid phase (stage 1) followed by a slower phase when severe desaturation develops (stage 2). Using a mathematical model incorporating pulmonary uptake dynamics, we found that elevated metabolic O_2 consumption accelerates $\dot{S}a_{O_2}$ throughout the entire desaturation process. By contrast, the remaining factors have a restricted temporal influence: low pre-apneic alveolar P_{O_2} causes an early onset of desaturation, but thereafter has little impact; reduced lung volume, hemoglobin content or cardiac output, accelerates $\dot{S}a_{O_2}$ during stage 1, and finally, total blood O_2 capacity (blood volume and hemoglobin content) alone determines $\dot{S}a_{O_2}$ during stage 2. Preterm infants with elevated metabolic rate, respiratory depression, low lung volume, impaired cardiac reserve, anemia, or hypovolemia, are at risk for rapid and profound apneic hypoxemia. Our insights provide a basic physiological framework that may guide clinical interpretation and design of interventions for preventing sudden apneic hypoxemia.

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Introduction

Apnea and its accompanying arterial O_2 desaturation are common clinical complications in preterm infants, occurring in more than 50% of very low birth weight infants [1]. In preterm infants, apnea causes a reduction in heart rate [2] and cerebral perfusion [3], often requires mechanical ventilation, and is associated with neurodevelopmental impairment [4]. Apnea-related hypoxemia is of major concern in light of evidence that repetitive hypoxia in newborn animals results in irreversibly-altered carotid body function [5], raising the possibility of impaired ventilatory control, and causes neurocognitive and behavioural deficits [6]. Respiratory arrest and hypoxemia are also strongly implicated in sudden infant death syndrome (SIDS) [7,8] where the speed at which hypoxemia develops is considered to be particularly dangerous.

In preterm infants, the rate of arterial O_2 desaturation ($\dot{S}a_{O_2}$) can be highly variable and rapid, with average rates as high as 4.3% s^{-1} during isolated apneas [9]. An earlier framework to describe $\dot{S}a_{O_2}$ proposed that metabolic O_2 consumption relative to alveolar volume determines the speed at which alveolar P_{O_2} falls [10]; it was envisaged that $\dot{S}a_{O_2}$ is then a function of falling P_{O_2} and the slope of the oxy-hemoglobin dissociation curve. However, such a model assumes that the rate of alveolar depletion of O_2, denoted pulmonary O_2 uptake ($\dot{V}p_{O_2}$), is equal to tissue O_2 consumption during apnea (see Methods – Theory). Previous studies in adults have shown that $\dot{V}p_{O_2}$ falls from metabolic consumption during apnea [11], and our previous modeling studies in lambs showed that the difference between $\dot{V}p_{O_2}$ and metabolic O_2 consumption has a crucial role in determining $\dot{S}a_{O_2}$ during recurrent apneas [12]. We found that apneic changes in $\dot{V}p_{O_2}$ cause desaturation to occur in 2 stages. During stage 1, lung O_2 stores are depleted, and $\dot{V}p_{O_2}$ falls below metabolic consumption. During stage 2, $\dot{V}p_{O_2}$ is close to zero, and tissue O_2 needs are provided by depletion of blood O_2 stores.

To date, no complete theoretical analysis of the factors influencing desaturation during apnea has been published. The only available study [13] has a number of critical limitations. First, the model incorporated a constraint of a fixed difference between Sa_{O_2} and mixed-venous saturation; thus dynamic changes in $\dot{V}p_{O_2}$ could not occur and their influence on $\dot{S}a_{O_2}$ could not be examined. Second, no assessment was made of the impact of cardiorespiratory factors on the two stages of O_2 desaturation. Third, in focusing on adults, the study did not examine profound desaturation to levels well below 60% as can often occur in preterm infants [9,14].

Accordingly, the aim of the current study was to quantify the importance of cardiorespiratory factors relevant to $\dot{S}a_{O_2}$ during apnea, with particular reference to the preterm infant. Using a model that permits variation of $\dot{V}p_{O_2}$ during apnea, we examine a number of factors known to influence $\dot{S}a_{O_2}$, such as lung volume [15], metabolic O_2 consumption [16] and pre-apneic arterial oxygenation [17] as well as factors that are particularly pertinent for

Author Summary

When breathing stops, the flow of O_2 into and the flow of CO_2 out of the body cease. Such an event, termed an apnea, can be especially dangerous in preterm infants in whom it can lead to a rapid decline in arterial O_2 saturation, reaching rates of 3–8% per second, rapidly reducing O_2 to a level that could lead to neurological damage. Despite extensive experimental research, we have a poor mechanistic understanding of the causes of rapidly developing hypoxemia. We describe a new mathematical model that allows examination of the importance of the major cardiorespiratory factors that are likely to influence the speed at which arterial hypoxemia worsens during apnea. We found that high metabolic rate as well as reduced pre-apneic ventilation, lung volume, cardiac output, hemoglobin content, blood O_2 affinity, and blood volume accelerate the development of hypoxemia during apnea. Importantly, the cardiorespiratory factors that contribute to rapid hypoxemia are all pertinent to the preterm infant during early postnatal development. Thus the newborn is highly susceptible to rapid and severe desaturation, potentially explaining the propensity of preterm infants, particularly those with apnea, to neurological impairment.

the developing newborn, including anemia, hypovolemia, reduced O_2 affinity, and chronically and acutely reduced cardiac output. We use the results to develop a conceptual framework for the interpretation of mechanisms underlying rapid $\dot{S}a_{O_2}$ during apnea.

Results

Overview of the two-compartment model for gas exchange

To determine the independent influence of clinically relevant cardiorespiratory factors on $\dot{S}a_{O_2}$ during a single isolated apnea, we used a two-compartment lung-body mathematical model which incorporated realistic blood O_2 stores and gas exchange dynamics (Figure 1), as described in Methods – Mathematical model (a full list of symbols is provided in Table 1). We used published parameters for healthy preterm infants born at ~30 wk gestational age (Table 2); the values represent measurements taken at approximately term equivalent age when surprisingly rapid desaturation has been observed [9]. We also derive analytic solutions for $\dot{S}a_{O_2}$ to quantify the importance of cardiorespiratory factors on $\dot{S}a_{O_2}$ to obtain a detailed view of the arterial O_2 desaturation process, as described in Methods – Theory.

Pulmonary gas exchange dynamics during apnea

To examine changes in O_2/CO_2 exchange during apnea, a single apnea was imposed on the model. During apnea, changes in alveolar O_2 and CO_2 stores are not constant (Figure 2); importantly, alveolar P_{O_2} ($P_{A_{O_2}}$) did not continue to fall at its initial rate as governed by metabolic O_2 consumption ($\dot{V}_{O_2}$), but instead the rate of fall in $P_{A_{O_2}}$ was reduced as it approached mixed venous P_{O_2} ($P\bar{v}_{O_2}$), an observation also reflected in the falling $\dot{V}p_{O_2}$. As a result, two distinct phases for O_2 depletion can be seen, which we refer to as stage 1 and stage 2 [12]. During stage 1, $P_{A_{O_2}}$ fell rapidly and $\dot{V}p_{O_2}$ decreased and became dissociated from $\dot{V}_{O_2}$; during stage 2, with $\dot{V}p_{O_2}$ greatly reduced, both $P_{A_{O_2}}$ and $P\bar{v}_{O_2}$ fell together at a reduced rate. The two distinct phases were also observed for alveolar and arterial P_{CO_2} ($P_{A_{CO_2}}$, Pa_{CO_2}) although stage 1 for CO_2 was substantially shorter than that for O_2. Such an

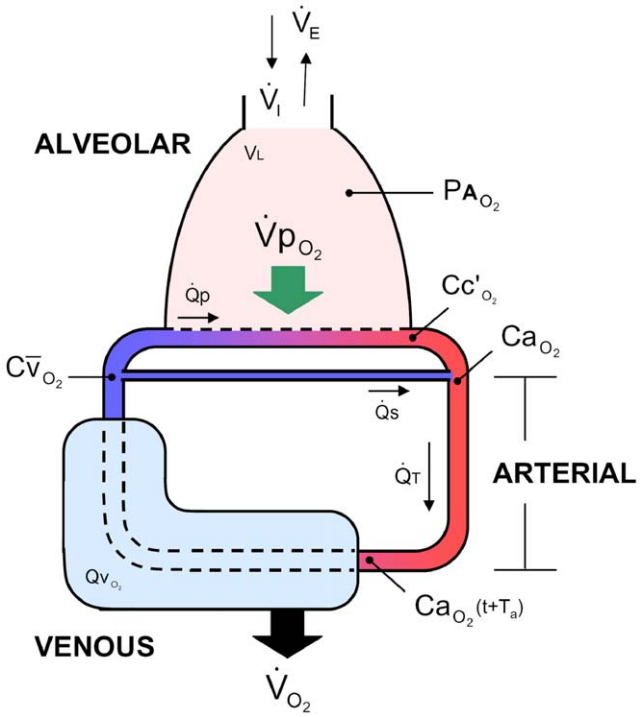

Figure 1. Model schematic representing O_2 uptake, transport and consumption. O_2 stores are represented by the alveolar, arterial, and venous compartments. Two dynamically-independent levels of O_2 uptake are denoted: pulmonary O_2 uptake ($\dot{V}p_{O_2}$) and metabolic consumption ($\dot{V}_{O_2}$). R-L shunt is also included. T_a is the arterial transit time. Symbols are described in Table 1.
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effect results from the earlier fall in pulmonary CO_2 uptake ($\dot{V}p_{CO_2}$) relative to the fall in $\dot{V}p_{O_2}$ (Figure 2A) and is reflected in the reduction in respiratory exchange ratio ($\dot{V}p_{CO_2}/\dot{V}p_{O_2}$) (Figure 2B). Consequently, a more rapid fall in $P_{A_{O_2}}$ was observed compared with the rise in $P_{A_{CO_2}}$(see Methods – Derivation of equations), such that $P_{A_{O_2}}$ fell by 100 mmHg in the time $P_{A_{CO_2}}$ rose by just 14 mmHg (Figure 2C).

Time-course of $\dot{S}a_{O_2}$ during apnea

The time-course of $\dot{S}a_{O_2}$ is complex (Figure 3), a consequence of the nonlinear O_2-dissociation curve in combination with the fall in $\dot{V}p_{O_2}$. At apnea onset, Sa_{O_2} started to fall with a rate equivalent to that predicted by Equation 12, where $\dot{S}a_{O_2} = 0.5\%\ s^{-1}$ (Figure 3). During apnea, changes in the slope of the O_2-dissociation curve ($\beta_{Hb_{O_2}}$) and $\dot{V}p_{O_2}$ dominated the time-course of desaturation as hypoxemia progressed. As Sa_{O_2} started to fall after apnea onset, $\beta_{Hb_{O_2}}$ increased with little change in $\dot{V}p_{O_2}$, resulting in a proportional increase in $\dot{S}a_{O_2}$. However, as arterial hypoxemia developed, there was a concurrent decline in $\dot{V}p_{O_2}$. As $\dot{S}a_{O_2}$ is directly proportional to the product $\beta_{Hb_{O_2}} \times \dot{V}p_{O_2}$ (Equation 11) it follows that during apnea, the peak $\dot{S}a_{O_2}$ of $3.5\%\ s^{-1}$ occurred when $\beta_{Hb_{O_2}} \times \dot{V}p_{O_2}$ reached a maximum. This occurred when neither $\dot{V}p_{O_2}$ nor $\beta_{Hb_{O_2}}$ was at its maximum (both ~50% of peak). Finally, with $\dot{V}p_{O_2}$ greatly reduced during stage 2, $\dot{S}a_{O_2}$ remained at a constant level ($\dot{S}a_{O_2} = 1.7\%\ s^{-1}$), close to that predicted by Equation 13 ($1.8\%\ s^{-1}$).

Factors influencing $\dot{S}a_{O_2}$

The following parameters were individually varied from their 'normal' values to quantify their influence on $\dot{S}a_{O_2}$: resting $P_{A_{O_2}}$,

Table 1. Mathematical symbols.

Symbol	Description
Ca_{CO_2}	Arterial CO_2 content
Ca_{O_2}	Arterial O_2 content
Cc'_{CO_2}	End-capillary arterial CO_2 content
Cc'_{O_2}	End-capillary arterial O_2 content
$C\bar{v}_{CO_2}$	Mixed venous CO_2 content
$C\bar{v}_{O_2}$	Mixed venous O_2 content
$\dot{C}\bar{v}_{CO_2}$	Rate of change in mixed venous CO_2 content
$\dot{C}\bar{v}_{O_2}$	Rate of change in mixed venous O_2 content
FI_{O_2}	Fractional inspired O_2
Fs	R-L pulmonary shunt fraction ($\dot{Q}p/\dot{Q}T$)
Hb	Hemoglobin content of blood
P_0	Barometric pressure, including conversion from STP to BTP, 863 mmHg
P_{50}	O_2 partial pressure at 50% saturation
P_{O_2}	O_2 partial pressure
Pa_{CO_2}	Arterial CO_2 partial pressure
Pa_{O_2}	Arterial O_2 partial pressure
$P_{A_{CO_2}}$	Alveolar CO_2 partial pressure
$P_{A_{N_2}}$	Alveolar N_2 partial pressure
$P_{A_{O_2}}$	Alveolar O_2 partial pressure
P_{vap}	Alveolar water vapour partial pressure, 47 mmHg
PB	Barometric pressure, 760 mmHg
Pc'_{CO_2}	End-capillary CO_2 partial pressure
Pc'_{O_2}	End-capillary O_2 partial pressure
$P_{I_{CO_2}}$	Inspired CO_2 partial pressure
$P_{I_{N_2}}$	Inspired N_2 partial pressure
$P_{I_{O_2}}$	Inspired O_2 partial pressure
$P\bar{v}_{O_2}$	Mixed venous O_2 partial pressure
$P\bar{v}_{CO_2}$	Mixed venous CO_2 partial pressure
$\dot{P}_{A_{CO_2}}$	Rate of change in alveolar CO_2 partial pressure
$\dot{P}_{A_{N_2}}$	Rate of change in alveolar N_2 partial pressure
$\dot{P}_{A_{O_2}}$	Rate of change in alveolar O_2 partial pressure
Qa	Arterial volume
Qb	Blood volume
Qb_{CO_2}	Blood volume for CO_2
Qb_{O_2}	Blood volume for O_2
Qv	Venous (and tissue) volume
Qv_{CO_2}	Venous (and tissue) volume for CO_2
Qv_{O_2}	Venous (and tissue) volume for O_2
$\dot{Q}T$	Cardiac output
$\dot{Q}p$	Pulmonary blood flow
RER	Respiratory exchange ratio ($\dot{V}p_{CO_2}/\dot{V}p_{O_2}$)
S_{O_2}	O_2 saturation
Sa_{O_2}	Arterial O_2 saturation
Sc'_{O_2}	End-capillary arterial O_2 saturation
$S\bar{v}_{O_2}$	Mixed venous O_2 saturation
$\dot{S}a_{O_2}$	Rate of arterial O_2 desaturation
$\dot{S}a_{O_2}^{10\ s}$	Average $\dot{S}a_{O_2}$ from t = 0–10 s during apnea
$\dot{S}a_{O_2}^{peak}$	Peak instantaneous ('linear') $\dot{S}a_{O_2}$ during apnea; stage 1
$\dot{S}a_{O_2}^{stage\ 2}$	$\dot{S}a_{O_2}$ during stage 2
$\dot{S}\bar{v}_{O_2}$	Rate of mixed-venous O_2 desaturation
T_a	Arterial transit time
VL	Lung volume
$\dot{V}_{CO_2}$	Metabolic CO_2 production
$\dot{V}_{O_2}$	Metabolic O_2 consumption
$\dot{V}E$	Expired alveolar ventilation
$\dot{V}I$	Inspired alveolar ventilation
$\dot{V}p_{CO_2}$	Pulmonary CO_2 uptake (from capillary to alveoli)
$\dot{V}p_{O_2}$	Pulmonary O_2 uptake (from alveoli to capillary)
$\dot{V}p_{total}$	Net pulmonary gas uptake from alveoli to capillary
βb_{CO_2}	Capacitance co-efficient of blood for CO_2
βb_{O_2}	Capacitance co-efficient of blood for O_2 relating changes in Pc'_{O_2} to changes in Cc'_{O_2}
$\beta_{Hb_{O_2}}$	Capacitance co-efficient of hemoglobin for O_2; slope of the O_2-dissociation curve relating changes in Pc'_{O_2} to changes in Sc'_{O_2}

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lung volume (VL), metabolic O_2 consumption ($\dot{V}_{O_2}$), blood hemoglobin content (Hb), cardiac output ($\dot{Q}T$), R-L shunt fraction (Fs), and the P_{O_2} at 50% saturation (P_{50}). All other parameters were kept constant to remove confounding effects, unless specified otherwise.

To quantify $\dot{S}a_{O_2}$ we used 3 different measures. First, since apnea is considered clinically significant if it lasts for >10 s and is accompanied by bradycardia or O_2 desaturation [18], we calculated the average rate of fall in Sa_{O_2} between apnea onset and 10 s later ($\dot{S}a_{O_2}^{10\ s}$); such a measure describes the immediacy of onset of desaturation and is analogous to the practical measurement of average $\dot{S}a_{O_2}$ used in many clinical studies [9,15,19,20]. Second, we determined the peak instantaneous $\dot{S}a_{O_2}$ during apnea

Table 2. Typical parameters for the preterm infant at term equivalent age.

Parameter	Value	Reference/s
Lung volume (VL)	20 ml kg^{-1}	[31,54]
Metabolic O_2 consumption ($\dot{V}_{O_2}$)	10 ml min^{-1} kg^{-1}	[55,39,40]
Cardiac output ($\dot{Q}T$)	250 ml min^{-1} kg^{-1}	[56]
Hemoglobin content (Hb)	8 g dl^{-1}	[22]
P_{50}	24 mmHg	[22]
Blood volume (Qb)	80 ml kg^{-1}	[57]

P_{50} is the partial pressure at 50% saturation. VL is taken from data on functional residual capacity. For all simulations unless otherwise stated: respiratory exchange ratio (RER) was assumed to be 0.8; shunt fraction (Fs) was adjusted to 8.7% to achieve a resting Pa_{O_2} of 72 mmHg as is typical for normal healthy infants [58]; resting alveolar ventilation ($\dot{V}I = 168$ ml $min^{-1} kg^{-1}$ under normal conditions) was set to achieve resting $P_{A_{O_2}} = 100$ mmHg.

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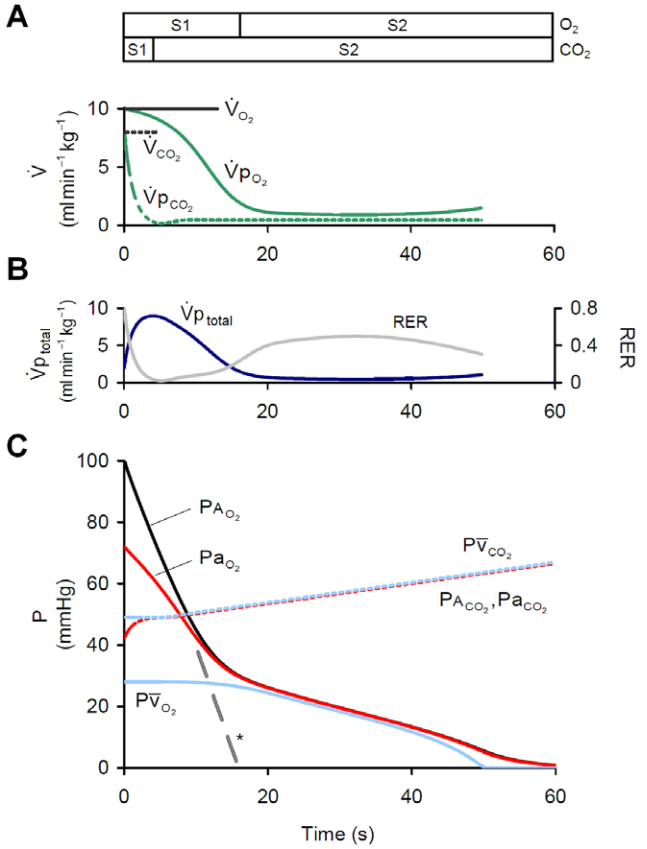

Figure 2. Pulmonary gas exchange during apnea. (A) Rate of pulmonary O_2/CO_2 exchange. $\dot{V}p_{O_2}$ and $\dot{V}p_{CO_2}$ fall from resting levels during apnea. (B) Net alveolar-capillary gas uptake ($\dot{V}p_{total} = \dot{V}p_{O_2} - \dot{V}p_{CO_2}$) and respiratory exchange ratio ($RER = \dot{V}p_{CO_2}/\dot{V}p_{O_2}$)during apnea. (C) Changes in alveolar, arterial and mixed venous P_{O_2}/P_{CO_2} during apnea. Contrast the time-course in $P_{A_{O_2}}$ and $P_{A_{CO_2}}$ as they fall/rise towards $P\bar{v}_{O_2}/P\bar{v}_{CO_2}$. (*) represents the fall in $P_{A_{O_2}}$ if $\dot{V}p_{O_2}$ was assumed equal to $\dot{V}_{O_2}$. S1 = stage 1; S2 = stage 2.
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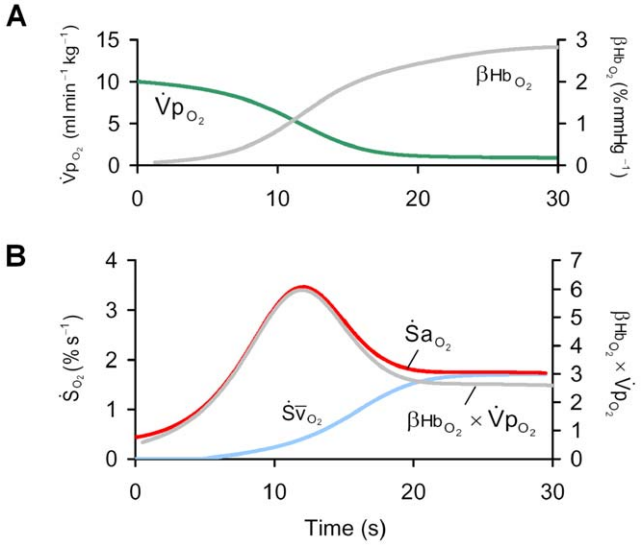

Figure 3. The time course of $\dot{S}a_{O_2}$ during apnea. Panel (A) shows the increase in the slope of the oxy-hemoglobin dissocation curve at the level of alveolar P_{O_2} ($\beta_{Hb_{O_2}}$), and the fall in pulmonary oxygen uptake ($\dot{V}p_{O_2}$) that occurs during apnea. Panel (B) shows that changes in the product $\beta_{Hb_{O_2}} \times \dot{V}p_{O_2}$ explain the time course of the instantaneous slope of arterial O_2 desaturation ($\dot{S}a_{O_2}$) during apnea. Note that the peak $\dot{S}a_{O_2}$ occurs when $\dot{V}p_{O_2}$ is substantially less than its resting value. Note also that the rate of fall of mixed-venous saturation ($\dot{S}\bar{v}_{O_2}$) and $\dot{S}a_{O_2}$ become equal and constant after 20 s.
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($\dot{S}a_{O_2}^{peak}$), the value during the linear portion of arterial desaturation [10,21] which we find is not confounded by resting Sa_{O_2}. Third, we report a measure of Sa_{O_2} during stage 2 apnea ($\dot{S}a_{O_2}^{stage\ 2}$). To quantify the sensitivity of $\dot{S}a_{O_2}$ to changes in each cardiorespiratory factor, we defined the term impact ratio as the ratio of proportional increase in $\dot{S}a_{O_2}$ to a small increase from the normal value of each factor. For example, an impact ratio of 1 indicates a one-to-one increase in $\dot{S}a_{O_2}$ with an increase in the factor, and a negative ratio indicates an inverse relationship. The impact of each cardiorespiratory factor on $\dot{S}a_{O_2}^{10\,s}$, $\dot{S}a_{O_2}^{peak}$, and $\dot{S}a_{O_2}^{stage\ 2}$ is summarised in Table 3.

Resting $P_{A_{O_2}}$. Changes in $P_{A_{O_2}}$, achieved via reduced resting ventilation or increasing inspired O_2 ($F_{I_{O_2}}$), had a substantial effect on the onset of desaturation. Reduced pre-apneic $P_{A_{O_2}}$ dramatically increased $\dot{S}a_{O_2}^{10\,s}$ (Figure 4A), but had little effect on $\dot{S}a_{O_2}^{peak}$ or $\dot{S}a_{O_2}^{stage\ 2}$. In contrast, increasing pre-apneic $P_{A_{O_2}}$ with the application of supplemental O_2 achieved the opposite, essentially right-shifting or delaying the arterial desaturation curve, where one second of delay can be achieved by an increase in $P_{I_{O_2}}$ ($\Delta P_{I_{O_2}}$) of ~7 mmHg, or $\Delta F_{I_{O_2}}$ of ~1% (see Methods – Derivation of equations). These results occurred despite only a minor influence being visible on resting Sa_{O_2}. For example, a reduction of $P_{A_{O_2}}$ from 100 to 60 mmHg caused a 6% reduction in resting Sa_{O_2} but at the same time led to a more than 2-fold elevation in $\dot{S}a_{O_2}^{10\,s}$ (Figure 4B). Additionally, a severe reduction in $P_{A_{O_2}}$, to below 70 mmHg, was required to elevate $\dot{S}a_{O_2}^{peak}$.

Lung volume (VL) and blood volume (Qb). $\dot{S}a_{O_2}^{10\,s}$ and $\dot{S}a_{O_2}^{peak}$ were inversely related to VL during stage 1 (Figure 5A, B), but changes in VL had no influence on $\dot{S}a_{O_2}^{stage\ 2}$. In direct contrast, reduced Qb strongly increased $\dot{S}a_{O_2}^{stage\ 2}$, but had no effect on stage

Table 3. Impact ratios describing the effect of cardiorespiratory factors on $\dot{S}a_{O_2}$.

Parameter alteration	$\dot{S}a_{O_2}^{10\,s}$	$\dot{S}a_{O_2}^{peak}$	$\dot{S}a_{O_2}^{stage\ 2}$
Resting $P_{A_{O_2}}$	−3.97	−0.35	−0.01
Lung volume (VL)	−2.24	−0.82	−0.09
Blood volume (Qb)	−0.01	−0.06	−0.68
O_2 consumption ($\dot{V}_{O_2}$) ^{CC}	+2.29	+1.00	+1.00
O_2 consumption ($\dot{V}_{O_2}$) ^{nCC}	+2.73	+1.92	+1.00
Hemoglobin content (Hb) ^{nCC}	−0.38	−1.00	−0.89
Hemoglobin content (Hb) ^{CC}	+0.01	−0.10	−0.89
P_{50}	+1.37	−0.68	−0.11
Cardiac output ($\dot{Q}_T$, resting)	−0.39	−0.90	0.00
Cardiac output ($\dot{Q}_T$, transient)	+1.45	−0.06	0.00
Shunt Fraction (Fs)	−0.01	+0.01	0.00

Impact ratio is defined as the ratio of proportional increase in $\dot{S}a_{O_2}$ to the proportional increase in each factor, based on small changes around normal values. An impact ratio of 1 indicates a one-to-one increase in $\dot{S}a_{O_2}$ >with an increase in the factor, and a negative ratio indicates an inverse relationship. CC = cardiac compensated, nCC = cardiac uncompensated.
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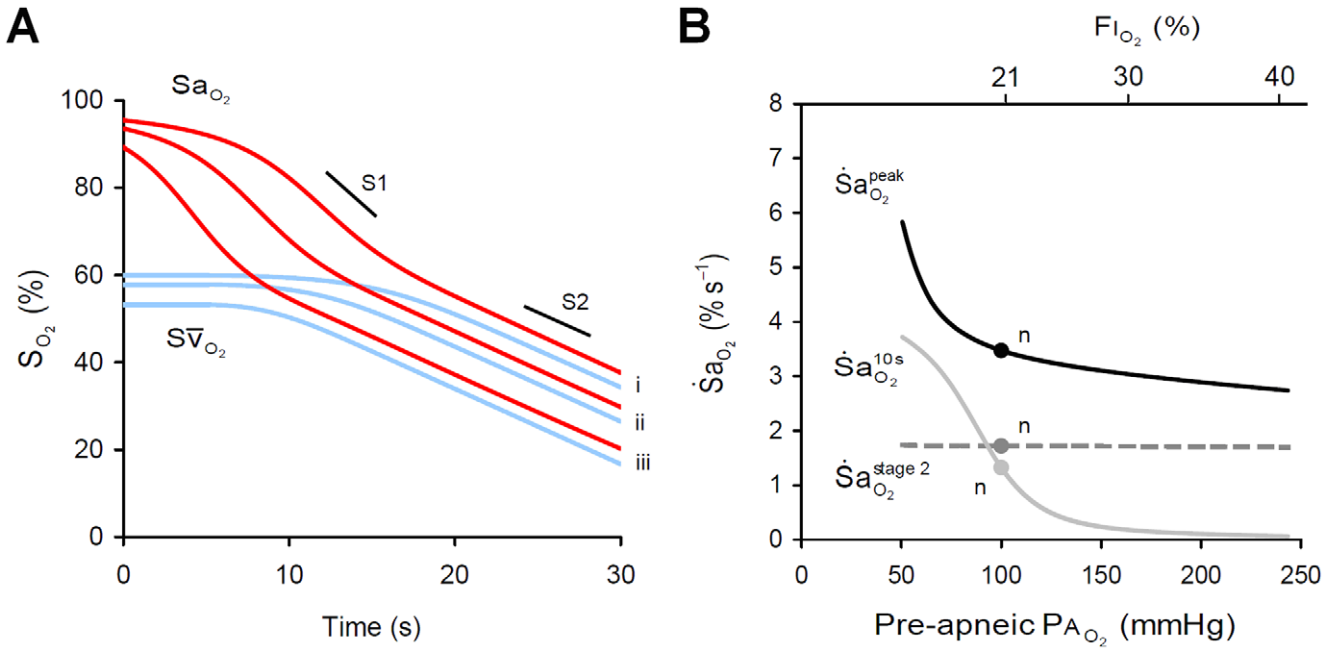

Figure 4. Impact of pre-apneic alveolar P_{O_2} (ventilation, supplemental O_2) on $\dot{S}a_{O_2}$. (A) Effect of three levels of alveolar P_{O_2}(PA_{O_2}), (i) 100 mmHg, (ii) 80 mmHg and (iii) 60 mmHg, on arterial (Sa_{O_2}) and mixed venous ($S\bar{v}_{O_2}$) O_2 desaturation during apnea. Note that arterial O_2 desaturation is substantially right-shifted with increased PA_{O_2}. (B) Sensitivity of $\dot{S}a_{O_2}$ to changes in pre-apneic PA_{O_2}(FI_{O_2}). Note that reduced PA_{O_2} has a major impact on $\dot{S}a_{O_2}^{10\,s}$ but little impact on $\dot{S}a_{O_2}^{stage\ 2}$; the influence on $\dot{S}a_{O_2}^{peak}$ is small in the normal range but becomes stronger at low PA_{O_2}. n = 'normal' 'values; S1, stage 1 slope; S2, stage 2 slope.
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1 desaturation as reflected in no change in $\dot{S}a_{O_2}^{peak}$ or $\dot{S}a_{O_2}^{10\,s}$ (Figure 5C, D).

Metabolic O_2 consumption ($\dot{V}_{O_2}$). To examine the impact of changing $\dot{V}_{O_2}$ on $\dot{S}a_{O_2}$, independent of resting $S\bar{v}_{O_2}$, $\dot{Q}T$ was adjusted to maintain resting $S\bar{v}_{O_2}$ constant, where $\Delta\dot{Q}T(\%) = \Delta\dot{V}_{O_2}(\%)$; we refer to this procedure as 'cardiac compensation'. Under this condition, elevated $\dot{V}_{O_2}$ caused a directly proportional increase in Sa_{O_2} throughout stages 1 and 2 (Figure 6A, B). Without cardiac compensation, the effect of increased $\dot{V}_{O_2}$ on Sa_{O_2} during stage 1 was magnified, as shown by the further increase in $\dot{S}a_{O_2}^{peak}$ (Figure 6A, B).

Hemoglobin content (Hb) and oxygen affinity (P_{50}). Reduced hemoglobin content (Hb) increased $\dot{S}a_{O_2}^{peak}$ and $\dot{S}a_{O_2}^{stage\ 2}$ but had little effect on $\dot{S}a_{O_2}^{10\,s}$ (Figure 7A, B). The increase in $\dot{S}a_{O_2}^{peak}$ occurred with an increase in the peak of the product $\beta_{Hb_{O_2}} \times \dot{V}p_{O_2}$ as $\dot{V}p_{O_2}$ was higher at each level of Sa_{O_2}. The simulation was repeated with cardiac compensation for the reduction in hemoglobin content, where $\Delta\dot{Q}T(\%) = 1/\Delta Hb(\%)$, to maintain constant resting $S\bar{v}_{O_2}$. Following such compensation, no changes in $\dot{S}a_{O_2}^{peak}$ or $\dot{S}a_{O_2}^{10\,s}$ were observed but reduced Hb continued to increase $\dot{S}a_{O_2}^{stage\ 2}$. In examining the influence of P_{50}, P_{90} was adjusted in equal proportion on the basis of published data [22]. Increased P_{50} increased the immediate $\dot{S}a_{O_2}$, increased $\dot{S}a_{O_2}^{10\,s}$, decreased $\dot{S}a_{O_2}^{peak}$ and had no effect on $\dot{S}a_{O_2}^{stage\ 2}$ (Figure 7C, D).

Cardiac output ($\dot{Q}T$). Reduced resting $\dot{Q}T$ increased $\dot{S}a_{O_2}^{peak}$, but had little impact on $\dot{S}a_{O_2}^{10\,s}$ or $\dot{S}a_{O_2}^{stage\ 2}$ (Figure 8A, B). As with Hb, the increase in $\dot{S}a_{O_2}^{peak}$ with reduced resting $\dot{Q}T$ occurred with an increase in the peak of the product $\beta_{Hb_{O_2}} \times \dot{V}p_{O_2}$. To differentiate between the influence on $\dot{S}a_{O_2}$ of an acute reduction in cardiac output, i.e. when bradycardia accompanies apnea, rather than a chronic reduction, we reduced cardiac output in a step-wise manner from the baseline value at the time of apnea onset. In constrast to the effect of reduced resting $\dot{Q}T$, a transient reduction in $\dot{Q}T$ decreased $\dot{S}a_{O_2}^{10\,s}$, but had a negligible impact on $\dot{S}a_{O_2}^{peak}$ or $\dot{S}a_{O_2}^{stage\ 2}$ (Figure 8C, D).

Resting R-L shunt fraction (Fs). Increased Fs reduced resting Sa_{O_2} and $S\bar{v}_{O_2}$ but had no effect on $\dot{S}a_{O_2}^{10\,s}$, $\dot{S}a_{O_2}^{peak}$, or $\dot{S}a_{O_2}^{stage\ 2}$ (Figure 9A, B).

Discussion

Our model analysis of the rate of arterial O_2 desaturation during apnea demonstrates that pre-apneic ventilation, lung volume, cardiac output, hemoglobin content and blood volume exert unique effects on $\dot{S}a_{O_2}$ throughout the time-course of desaturation, while metabolic O_2 consumption is uniformly influential throughout the process. Our analysis reveals that lung volume and the slope of the O_2-dissociation curve are important early in the process, during what we refer to as stage 1 [12], but not stage 2. For the first time, our study reveals that reduced cardiac output and hemoglobin content, and as a consequence resting mixed-venous saturation, substantially accelerate peak $\dot{S}a_{O_2}$. Finally, low blood volume and hemoglobin content, and therefore a low total blood O_2 capacity, increase the speed of desaturation, but only in stage 2. In addition to infants with elevated metabolic needs and low lung volume, those with anemia, cardiac dysfunction, or hypovolemia, which are common complications of prematurity, are at heightened risk of rapid and profound arterial desaturation during apnea.

Methodological considerations

To evaluate the independent effects of cardiorespiratory factors on $\dot{S}a_{O_2}$ we used a two-compartment model, incorporating both alveolar and blood gas stores. The inclusion of a realistic blood store was crucial to reveal that changes in $\dot{V}p_{O_2}$ occur as a consequence of arterial and mixed-venous saturation falling

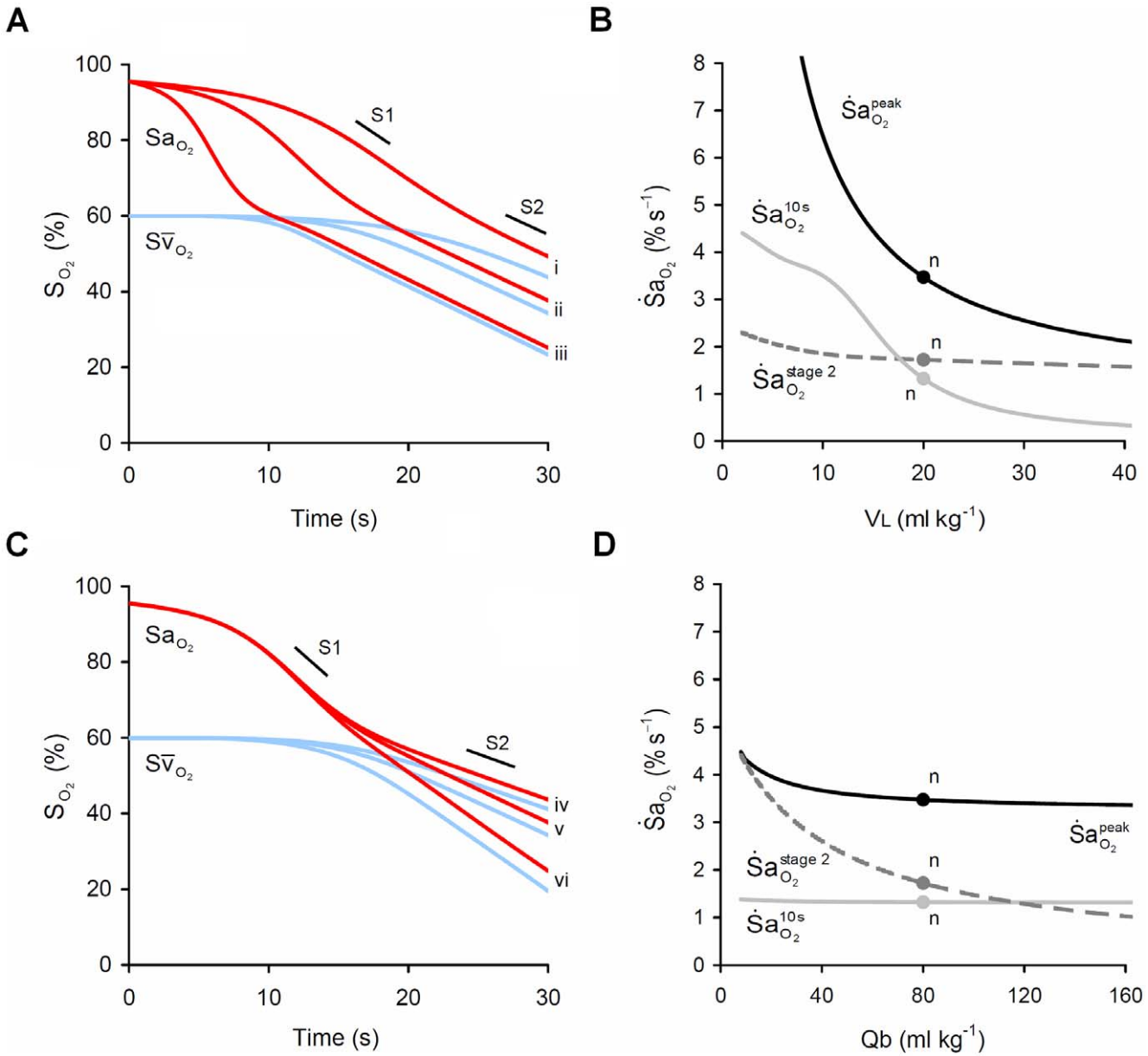

Figure 5. Impact of lung volume (V_L) and blood volume (Qb) on $\dot{S}a_{O_2}$. (A) Effect of three levels of V_L, (i) 30, (ii) 20 and (iii) 10 ml kg^{-1}, on arterial (Sa_{O_2}) and mixed venous ($S\bar{v}_{O_2}$) O_2 desaturation during apnea. (B) Sensitivity of $\dot{S}a_{O_2}$ to changes in V_L. Note that reduced V_L has a strong impact on $\dot{S}a_{O_2}^{peak}$ and $\dot{S}a_{O_2}^{10\,s}$ but no impact on $\dot{S}a_{O_2}^{stage\ 2}$. (C) Effect of three levels of Qb, (iv) 120, (v) 80 and (iv) 40 ml kg^{-1}, on Sa_{O_2} and $S\bar{v}_{O_2}$ during apnea. (D) Sensitivity of $\dot{S}a_{O_2}$ to changes in Qb. Note that reduced Qb has little impact on $\dot{S}a_{O_2}^{peak}$ or $\dot{S}a_{O_2}^{10\,s}$ but has a large impact on $\dot{S}a_{O_2}^{stage\ 2}$. n = 'normal' values; S1, stage 1 slope; S2, stage 2 slope.
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asynchronously during apnea (Figure 3). Our approach allowed us to extend the previous framework based on the assumption of constant $\dot{V}p_{O_2}$ [23], which prevented the recognition that a steep O_2-dissociation curve and low lung volume do not accelerate $\dot{S}a_{O_2}$ beyond stage 1. Furthermore, the varying $\dot{V}p_{O_2}$ permitted recognition that cardiac output, hemoglobin content, and blood volume have a major influence on $\dot{S}a_{O_2}$.

In the current study, the typical value of $\dot{S}a_{O_2}$ found using our model was 3.5% s^{-1} whereas Poets and Southall [9] using beat-by-beat oximetry in preterm infants reported a mean value for $\dot{S}a_{O_2}$ = 4.3% s^{-1} during isolated apneas. Reasons for our lower value may lie with our simplifying assumptions. Notably, we assumed a homogenous lung compartment and complete gas mixing and as such, the model incorporated neither limitation of alveolar-capillary diffusion nor an uneven ventilation-perfusion distribution, two factors that could cause an increase in $\dot{S}a_{O_2}$. In addition, we assumed a constant lung volume during apnea, equal to published values of functional residual capacity, whereas it is known that lung volume can fall during apnea [15,24]; based on our data, a fall in lung volume to 15.5 ml $min^{-1}kg^{-1}$ immediately after apnea onset would achieve $\dot{S}a_{O_2}$ of 4.3% s^{-1} (Figure 5B).

A final assumption implicit in our model is that all O_2 transfer to the blood occurs via the pulmonary circulation. However, in very preterm infants there is evidence of percutaneous respiration in the first few days of life in both room air and with supplemental O_2 [25]. With whole body exposure of 90% O_2 to the newborn skin, it

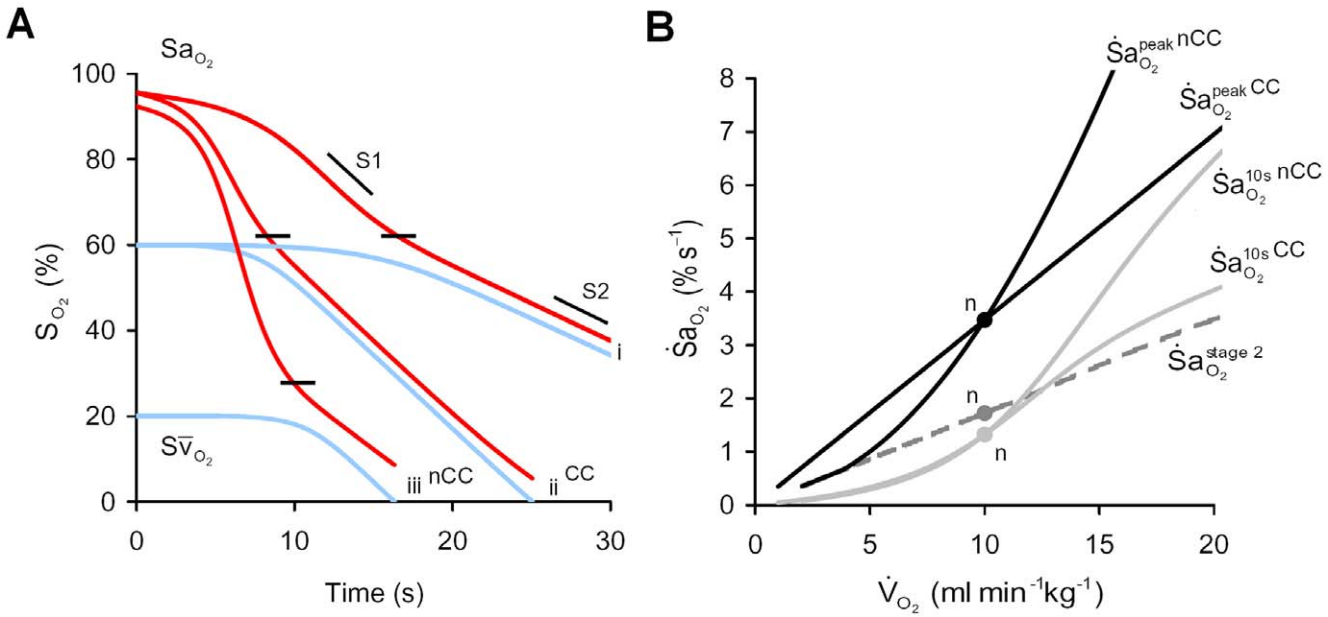

Figure 6. Impact of metabolic O_2 consumption ($\dot{V}_{O_2}$) on $\dot{S}a_{O_2}$. Panel (A) shows the effect of doubling $\dot{V}_{O_2}$ on arterial (Sa_{O_2}) and mixed venous ($S\bar{v}_{O_2}$) O_2 during apnea; (i) 10 ml $min^{-1}kg^{-1}$, (ii) 20 ml $min^{-1}kg^{-1}$ with cardiac compensation (CC), and (iii) 20 ml $min^{-1}kg^{-1}$ with no CC (nCC). Note that with CC, increased $\dot{V}_{O_2}$, from (i) to (ii), elevated $\dot{S}a_{O_2}$ uniformly at all levels of Sa_{O_2} during both stages 1 and 2; note that the level of Sa_{O_2} at the inflection point (shown by short black lines) is unchanged. With nCC (iii), increased $\dot{V}_{O_2}$ caused a reduced resting $S\bar{v}_{O_2}$ and lower Sa_{O_2} inflection, and greater $\dot{S}a_{O_2}$ during stage 1, compared to (ii). (B) Sensitivity of $\dot{S}a_{O_2}$ to changes in $\dot{V}_{O_2}$. Note that with increased $\dot{V}_{O_2}$: a uniform increase in $\dot{S}a_{O_2}^{peak}$ occurred with CC, and a more-than-proportional increase was seen with nCC; $\dot{S}a_{O_2}^{10\,s}$ is elevated in both cases, but more so with nCC; a uniform increase in $\dot{S}a_{O_2}^{stage\ 2}$ is shown regardless of CC. n = 'normal' values; S1, stage 1 slope; S2, stage 2 slope.
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has been calculated that $\dot{V}p_{O_2}$ can be reduced by 8–10% [26], likely via an increased resting mixed-venous saturation; our study demonstrates that such an effect would decrease $\dot{S}a_{O_2}$ during apnea.

Pulmonary gas exchange dynamics during apnea

Our study is consistent with previous observations that $\dot{V}p_{O_2}$ and $\dot{V}p_{CO_2}$ rapidly decline during apnea from their steady-state values [11], with $\dot{V}p_{CO_2}$ falling faster than $\dot{V}p_{O_2}$. The relatively low blood capacitance for O_2 compared with that for CO_2 results in the resting alveolar–mixed-venous partial pressure difference being ~12-fold greater for O_2 than for CO_2. Consequently, when apnea begins ~12 times more O_2 than CO_2 must diffuse across the lung to obliterate the alveolar–mixed-venous partial pressure difference. The slower fall in $\dot{V}p_{O_2}$ vs. $\dot{V}p_{CO_2}$ provides for a faster depletion of alveolar O_2 vs. CO_2 stores; such an effect results in complete desaturation of arterial blood in the time Pa_{CO_2} rises by just 14 mmHg. These findings lead us to conclude that short-term O_2 homeostasis is more unstable than CO_2 homeostasis and thus that the danger of isolated apneas in infants is likely to be mediated via hypoxemia rather than hypercapnia.

Factors influencing $\dot{S}a_{O_2}$

Our study provides for the first time a comprehensive analysis of the factors that determine arterial desaturation during apnea in preterm infants. We show that resting oxygenation in the form of alveolar P_{O_2} has the greatest influence on desaturation at apnea onset. When apnea begins at an increasingly lower alveolar P_{O_2}, $\dot{S}a_{O_2}$ more quickly reaches its maximum because P_{O_2} rapidly arrives at the steepest part of the O_2-dissociation curve. This effect explains the inverse relationship between mean $\dot{S}a_{O_2}$ and pre-apneic Sa_{O_2} during apnea [17], but as we show the peak slope itself is negligibly affected by reduced resting P_{O_2} within the normal range.

We demonstrate that $\dot{S}a_{O_2}$ is inversely related to lung volume during stage 1 of apnea as a result of the greater reduction in alveolar P_{O_2} in poorly inflated lungs per unit of O_2 transferred into the pulmonary capillaries. This analysis is consistent with the inverse correlation between $\dot{S}a_{O_2}$ and lung volume [15], with the view that active upper airway closure maintains lung volume and slows $\dot{S}a_{O_2}$ [27,28], and with our recent report that the application of continuous positive airway pressure effectively slows $\dot{S}a_{O_2}$ in lambs [29]. However, once stage 2 begins, the blood becomes the principal source of O_2 and thus the only store which influences $\dot{S}a_{O_2}$.

A novel finding from our study is that reduced resting mixed-venous saturation, caused by either a reduced cardiac output or reduced hemoglobin content, strongly elevates peak $\dot{S}a_{O_2}$, independent of metabolic O_2 consumption. We show that reduced resting mixed-venous saturation accelerates $\dot{S}a_{O_2}$ via an increase in the peak value of $\beta_{Hb_{O_2}} \times \dot{V}p_{O_2}$; in other words, low mixed-venous saturation provides for a greater pulmonary O_2 uptake even in the presence of a developing arterial hypoxemia, and thereby increases $\dot{S}a_{O_2}$. A role for hemoglobin in determining $\dot{S}a_{O_2}$ is consistent with the finding that elevated hemoglobin content in adults slows $\dot{S}a_{O_2}$ during apnea [21]. In contrast, blood transfusion to raise hemoglobin content in anemic preterm infants, a common clinical therapy, has little or no impact on the severity of apneic desaturation [30]. Our proposed explanation for the lack of benefit of raising hemoglobin content via transfusion is that it also reduces heart rate [30] and cardiac output. Thus, in the newborn, the rise in mixed-venous saturation expected after transfusion is counteracted by a tendency for mixed-venous saturation to fall as a result of reduced cardiac output. An investigation that failed to find an effect of cardiac output on $\dot{S}a_{O_2}$ [23] did not account for our

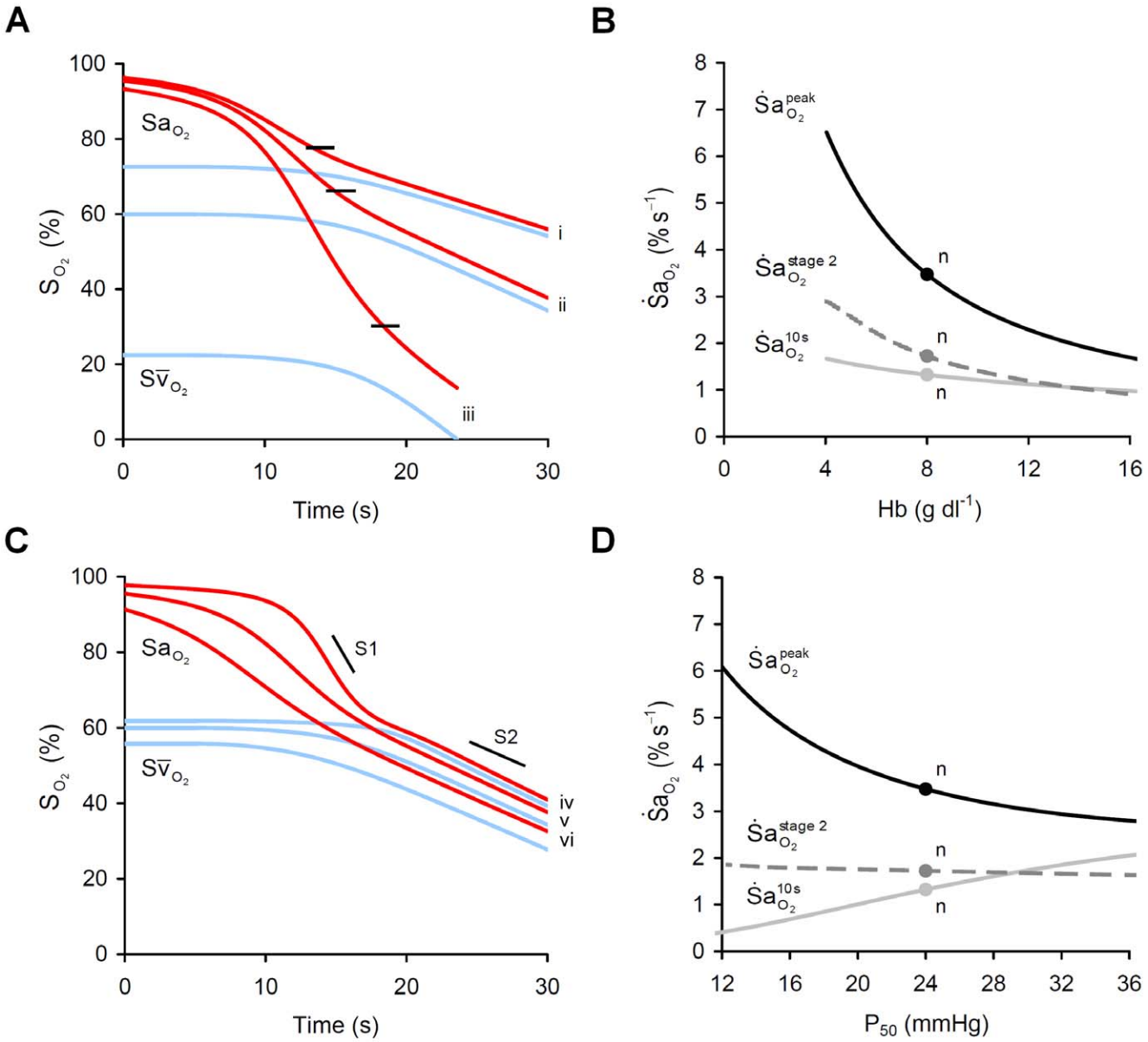

Figure 7. Impact of hemoglobin content (Hb) and O_2 affinity (P_{50}) on $\dot{S}a_{O_2}$. (A) Effect of three levels of Hb, (i) 12 g dl^{-1}, (ii) 8 g dl^{-1} and (iii) 4 g dl^{-1}, on arterial (Sa_{O_2}) and mixed venous ($S\bar{v}_{O_2}$) O_2 desaturation during apnea. Note the fall in Sa_{O_2} at the inflection point (shown by short black lines). Note also that the reduced Hb has little impact on desaturation above $Sa_{O_2} = 80\%$. (B) Sensitivity of $\dot{S}a_{O_2}$ to changes in Hb. (C) Effect of three levels of P_{50}, (iv) 18 mmHg, (v) 24 mmHg, and (vi) 36 mmHg, on $\dot{S}a_{O_2}$. (D) Sensitivity of $\dot{S}a_{O_2}$ to changes in P_{50}. n = 'normal' values; S1, stage 1 slope; S2, stage 2 slope.
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finding that pre-apneic and transient changes in cardiac output have opposing influence on $\dot{S}a_{O_2}$. Importantly, we find that a transient fall in cardiac output, characteristic of bradycardia during apnea in preterm infants [2], conserves alveolar O_2 via reduced $\dot{V}p_{O_2}$ and thus reduces $\dot{S}a_{O_2}$ (see Equations 10 and 11). Consistent with this finding, apneic bradycardia prevents a rapid fall in Sa_{O_2} in adults [21].

We found that each of the factors examined exerts a unique and therefore recognisable influence on the time course of the desaturation process (Figure 10). Low alveolar P_{O_2} can be recognised by a left-shift of the desaturation trajectory so that desaturation begins sooner following the onset of apnea. A steep desaturation slope in the early phase of stage 1 points to a low ratio of lung volume to metabolic O_2 consumption. In the late phase of stage 1, when desaturation proceeds in a linear fashion, a low resting mixed-venous saturation accelerates $\dot{S}a_{O_2}$ and leaves the fingerprint of a low inflection point in arterial O_2 desaturation; low resting mixed-venous saturation reflects low cardiac output or hemoglobin content with respect to O_2 consumption. Lastly rapid $\dot{S}a_{O_2}$ during stage 2 signifies a low total blood O_2 capacity with respect to O_2 consumption which would point to either low blood volume or anemia. The presence of a constant R-L shunt, while having no influence on $\dot{S}a_{O_2}$, causes a parallel downwards shift in the desaturation trajectory. The unique impact of different factors on the desaturation curve may be used to guide preventive clinical intervention.

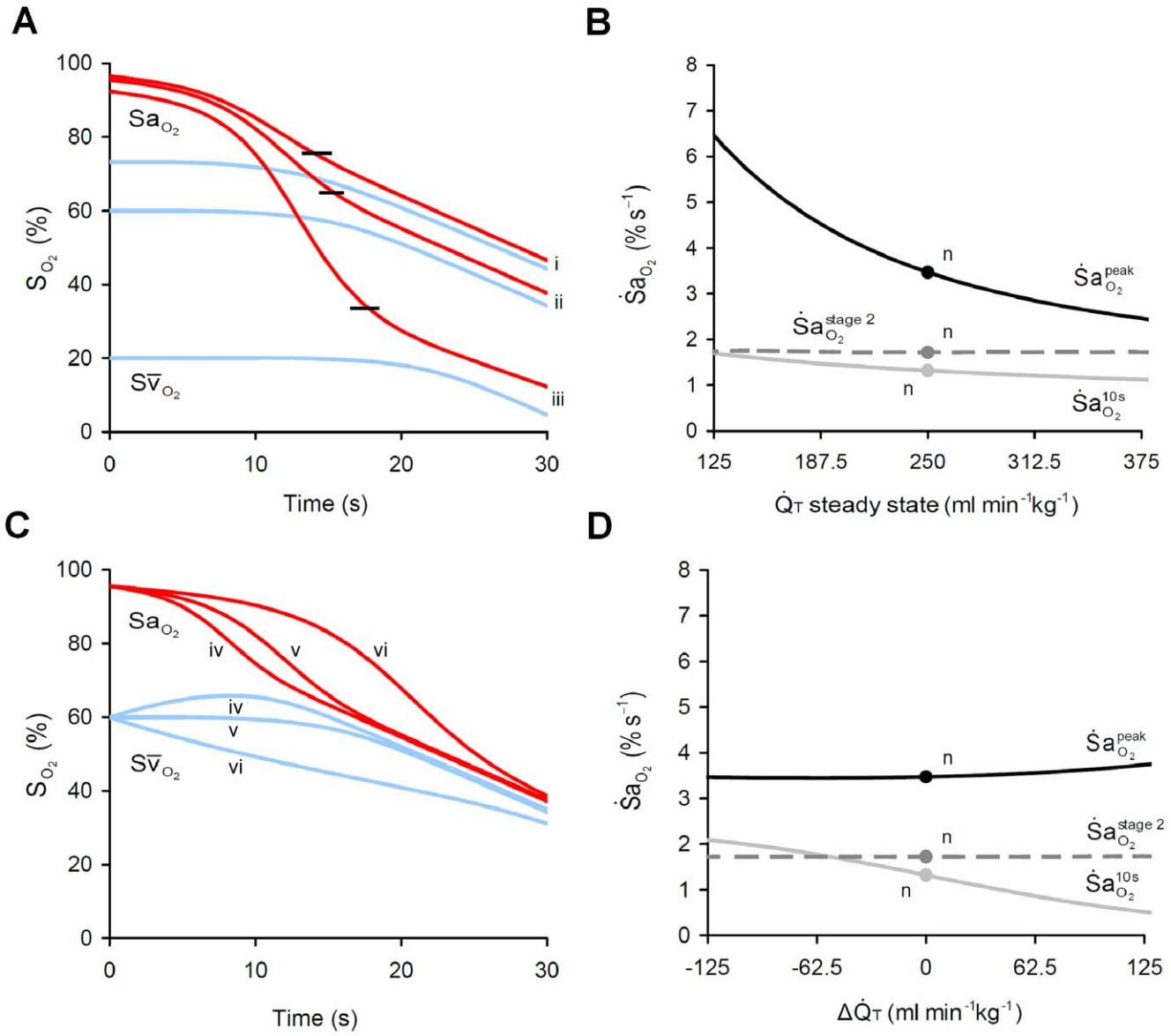

Figure 8. Impact of cardiac output ($\dot{Q}_T$) on $\dot{Sa}_{O_2}$. (A) Effect of three levels of resting $\dot{Q}_T$, (i) 375 ml min^{-1}kg^{-1}, (ii) 250 ml min^{-1}kg^{-1}, and (iii) 125 ml min^{-1}kg^{-1}, on arterial (Sa_{O_2}) and mixed venous ($S\bar{v}_{O_2}$) O_2 during apnea. Note that reduced $\dot{Q}_T$ elevates $\dot{Sa}_{O_2}$, associated with a reduction in resting $S\bar{v}_{O_2}$ and reduction in Sa_{O_2} at the stage 1–2 transition or inflection point (shown by short black lines). (B) Sensitivity of $\dot{Sa}_{O_2}$ to changes in $\dot{Q}_T$. Note the strong influence of $\dot{Q}_T$ on $\dot{Sa}_{O_2}^{peak}$, but negligible effect on $\dot{Sa}_{O_2}^{10\,s}$ and $\dot{Sa}_{O_2}^{stage\ 2}$. (C) Simulations in (A) repeated for a step change in $\dot{Q}_T$ at apnea onset by (iv) +125 ml min^{-1}kg^{-1} (e.g. tachycardia), (v) 0 ml min^{-1}kg^{-1}, and (vi) −125 ml min^{-1}kg^{-1} (e.g. bradycardia), following resting $\dot{Q}_T$ = 250 ml min^{-1}kg^{-1}. Note that the transient effect of $\dot{Q}_T$ is opposite to the resting effect of $\dot{Q}_T$ on arterial desaturation during apnea. (D) Sensitivity of $\dot{Sa}_{O_2}$ to acute changes in $\dot{Q}_T$ during apnea. Note the strong influence of a step-change in $\dot{Q}_T$ on $\dot{Sa}_{O_2}^{10\,s}$, but negligible effect on $\dot{Sa}_{O_2}^{peak}$ and $\dot{Sa}_{O_2}^{stage\ 2}$. n = 'normal' values.
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Clinical significance

We show theoretically that the lower lung volume [31] and higher metabolic O_2 consumption [32] of preterm compared to term infants predisposes to a rapid onset and progression of desaturation during apnea. Two reports offer support for this view. First, rapid desaturation occurs in infants with low functional residual capacity [15], a finding that may help to explain the more frequent O_2 desaturation events during active sleep [33] when functional residual capacity is reduced. Second, frequent desaturation is characteristic of preterm infants with bronchopulmonary dysplasia (BPD) [34] whose O_2 consumption is 25% greater [35], and functional residual capacity is 25% less [36], than in preterm infants without BPD; Equations 11 and 12 predict that such differences increase both immediate and peak $\dot{Sa}_{O_2}$ by ~70%. In addition, hypoventilation and reduced resting $P_{A_{O_2}}$ in infants with BPD, as inferred from elevated $P_{A_{CO_2}}$ [37], further increase desaturation at apnea onset. Our finding that each rise of 1% in inspired O_2 provides ~1 s of delay (right-shift) in the onset of apneic desaturation (Equation 15) may guide the titration of supplemental O_2 for the prevention of apneic hypoxemia while minimising the well known side-effects of long-term exposure to hyperoxia.

Our study has implications for the management of infants in clinical care. Metabolic O_2 consumption can be elevated after

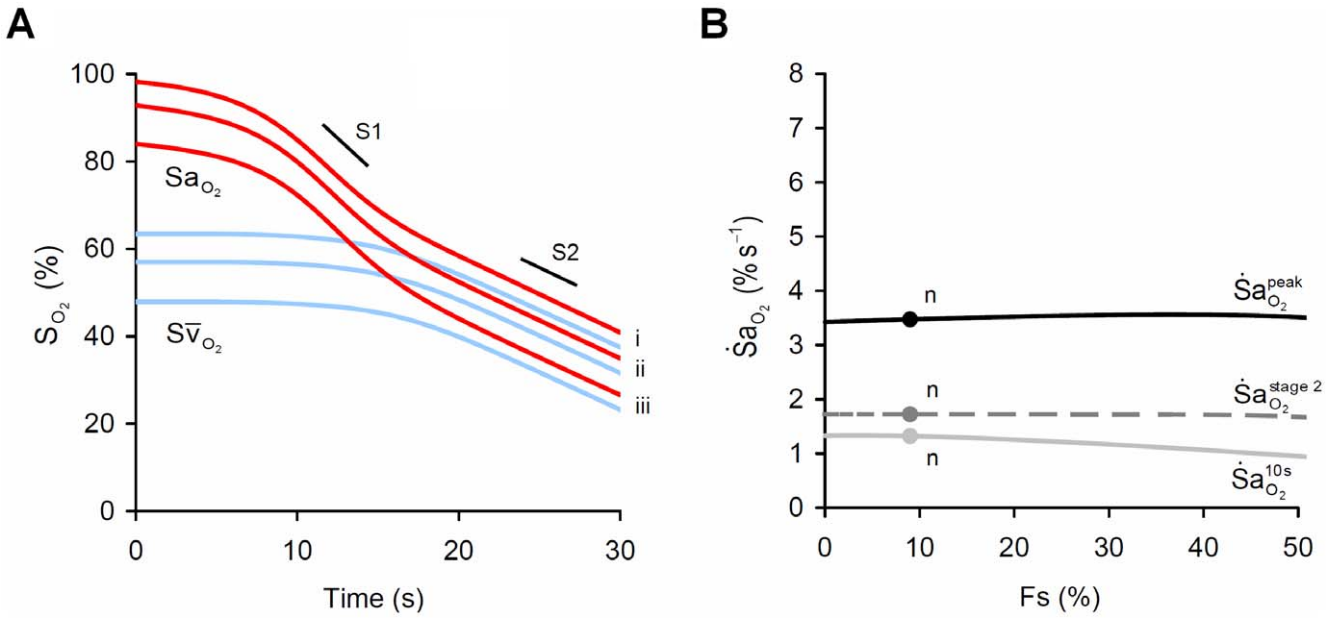

Figure 9. Impact of R-L shunt (Fs) on $\dot{S}a_{O_2}$. (A) Effect of three levels of Fs, (i) 0%, (ii) 15%, and (iii) 30%, on arterial (Sa_{O_2}) and mixed venous ($S\bar{v}_{O_2}$) O_2 during apnea. Note that resting R-L shunt fraction has a negligible impact on $\dot{S}a_{O_2}$ during apnea. (B) Sensitivity of $\dot{S}a_{O_2}$ to changes in Fs. n = 'normal' values; S1, stage 1 slope; S2, stage 2 slope.
doi:10.1371/journal.pcbi.1000588.g009

feeding [38], with reduced ambient temperature [39], and via the adminstration of methylxanthines [40]. Despite the success of methylxanthines in reducing the frequency of apnea and bradycardia, such treatment has surprisingly little impact on hypoxemic episodes [41]; we suggest that the elevated O_2 consumption and the absence of bradycardia are likely to increase $\dot{S}a_{O_2}$ during those apneas that persist despite treatment. The severity of hypoxemic episodes is reduced by switching preterm infants from supine to prone [42], which may increase functional residual capacity [43] and improve diaphragm function, increase tidal volume and increase resting alveolar P_{O_2} [44]. Our finding that low cardiac output leads to increased $\dot{S}a_{O_2}$ during apnea leads to the suggestion that judicious adjustment of inotropic support in infants with cardiac abnormalities could improve resting mixed-venous saturation and reduce apneic hypoxemia.

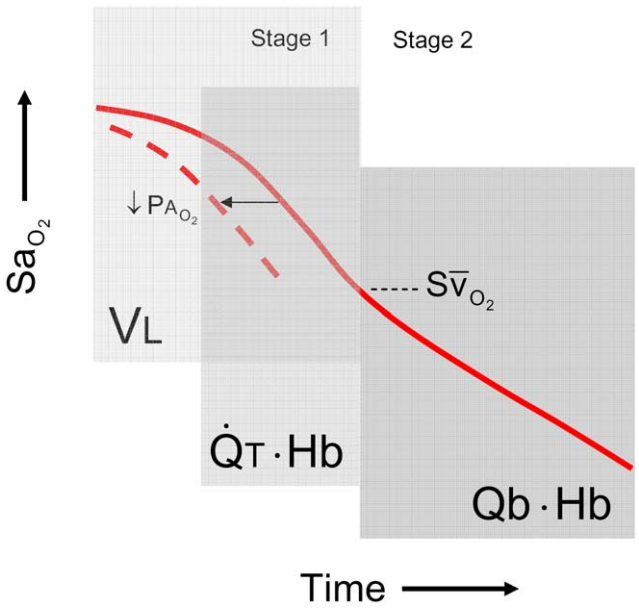

Figure 10. Conceptual framework depicting the temporal sequence of influence of the key cardiorespiratory factors on $\dot{S}a_{O_2}$. Note the regions of influence of lung volume (VL), cardiac output ($\dot{Q}T$) and blood volume (Qb), each with respect to metabolic O_2 consumption ($\dot{V}_{O_2}$). Hemoglobin content (Hb) influences the latter phase of stage 1 as well as stage 2. The impact of reduced VL is limited to stage 1, and blood volume to stage 2. Reduced $P_{A_{O_2}}$ causes a leftward shift in the desaturation trajectory. Note that the point of inflection at the transition between stages reveals the resting $S\bar{v}_{O_2}$.
doi:10.1371/journal.pcbi.1000588.g010

Hypoxemic events become less frequent between infancy and childhood, despite an unchanged apnea frequency [28], perhaps as a result of a fall in O_2 consumption per body weight. However, before this occurs, infants experience a period of susceptibility to rapid desaturation during apnea as a result of a fall in hemoglobin content and O_2 affinity [22] and a rise in O_2 consumption [45]. The implications for SIDS are obvious in that these changes coincide with the peak incidence for SIDS at 2–3 months [46]. SIDS also occurs disproportionately in preterm infants [46], who manifest severe anemia [22] and greater O_2 consumption. Infants resuscitated from apparent life threatening events have been found to have lower hemoglobin content [47], pointing to a potential role for rapid $\dot{S}a_{O_2}$ in the progression of such events. It is possible that the rapid development of apneic hypoxemia initiates prolonged hypoxic cardiorespiratory depression that in turn leads to SIDS.

Conclusion

We have provided a mathematical framework for quantifying the relative importance of key cardiorespiratory factors on the rate of arterial O_2 desaturation during apnea, with particular relevance to preterm infants. For the first time we have demonstrated that each of the factors examined has a signature influence on the trajectory of desaturation, providing quantitative insight into the causes of rapidly developing hypoxemia during apnea.

Methods

Mathematical model

Lung compartment. For the lung, a single homogeneous compartment is assumed based on the model of Grodins et al [48]. Each equation describing changes in the alveolar partial pressure of each gas (G) is based on the conservation of mass (specifically, the pressure–volume product) and is expressed in terms of inspired and expired alveolar ventilation and transfer of gases into the pulmonary capillary:

$$\dot{P}_{A_G} = \frac{\dot{V}_I P_{I_G} - \dot{V}_E P_{A_G} - P_0 \dot{V}p_G}{V_L} \quad (1)$$

where $\dot{P}_{A_G}$ represents the rate of change of alveolar P_{O_2}, P_{CO_2}, and P_{N_2}; P_{I_G} represents the inspired alveolar partial pressure of each gas G; P_0 is atmospheric pressure converted from STP to BTP (863 mmHg); $\dot{V}p_G$ represents $\dot{V}p_{O_2}$ and $-\dot{V}p_{CO_2}$, pulmonary gas uptake (STPD) for O_2 and CO_2 ($\dot{V}p_{N_2}$ was neglected in this study for simplicity); $\dot{V}_I$ and $\dot{V}_E$ are inspired and expired alveolar ventilation (BTPS). Accounting for the difference in $\dot{V}_E$ and $\dot{V}_I$ due to a net pulmonary gas uptake into the pulmonary blood, yields:

$$\dot{V}_E = \dot{V}_I - \frac{P_0}{P_B - P_{vap}} \dot{V}p_{total} \quad (2)$$

where P_B = barometric pressure (760 mmHg); P_{vap} = water vapour pressure (47 mmHg); $\dot{V}p_{total}$ is the net pulmonary gas uptake, $\dot{V}p_{total} = \dot{V}p_{O_2} - \dot{V}p_{CO_2}$.

Since purely obstructive apneas are relatively rare in preterm infants [49], an unobstructed airway was chosen as the standard model in this study. In the current study it was assumed that lung volume did not fall during apnea, as in active sleep [24], when apneic desaturation events are most common [33]. With lung volume constant, conservation of mass requires that passive airflow into the unobstructed airway must occur in response to a net pulmonary gas uptake into the pulmonary blood [11]. To account for this effect, we can write:

$$\dot{V}_I = \frac{P_0}{P_B - P_{vap}} \dot{V}p_{total} \quad (3)$$

Pilot simulations predicted that the volume of gas inflow during apnea is unlikely to exceed physiological deadspace. Thus, during apnea P_{I_G} is taken as P_{A_G} of the last exhaled breath prior to apnea onset.

For the current study we assumed diffusion equilibrium at the pulmonary capillaries, such that $P_{A_G} = Pc'_G$. Gas uptake is determined from the Fick equation; specifically, pulmonary blood flow ($\dot{Q}p$), and the difference between end capillary (Cc'_G) and mixed venous ($C\bar{v}_G$) content:

$$\dot{V}p_G = \dot{Q}p(Cc'_G - C\bar{v}_G) \quad (4)$$

Utilising equations for R-L shunt, arterial content of each gas G is determined from its end capillary (Cc'_G) and mixed venous ($C\bar{v}_G$) content, and pulmonary shunt fraction (Fs):

$$Ca_G = (1 - Fs)Cc'_G + (Fs)C\bar{v}_G \quad (5)$$

Fs defines the ratio of pulmonary blood flow to cardiac output, such that $Fs = (1 - \dot{Q}p)/\dot{Q}_T$.

Body compartment. Assuming that the P_{O_2} of the venous blood is equilibrated with the tissue P_{O_2}, the mass-balance equations are:

$$\dot{C}\bar{v}_G = \frac{\dot{Q}_T[Ca_G(t - T_a) - C\bar{v}_G] - \dot{V}_G}{Qv_G} \quad (6)$$

where $Ca_G(t - T_a)$ represents the gas content of O_2 and CO_2 in the arterioles; T_a is arterial transit time; $\dot{V}_G$ represents $\dot{V}_{O_2}$ and $-\dot{V}_{CO_2}$, the metabolic consumption of O_2 and production of CO_2; Qv_G represents Qv_{O_2} and Qv_{CO_2} the combined venous/tissue volumes for O_2 and CO_2.

Blood O_2 stores were partitioned by assigning blood volume (Qb) to arterial (25%) and venous (75%) compartments [50] and they were modelled assuming an entirely unmixed arterial compartment, and an entirely mixed and homogenous venous compartment. The arterial transit time (T_a) is constrained by the arterial volume (Qa) by the relationship $T_a = Qa/\dot{Q}_T$. The body compartment volume Qv_{O_2} is taken as the venous volume. Qv_{CO_2}, the effective venous/tissue volume for CO_2 is taken as the same value for Qv_{O_2}, based on published data (see Methods – Derivation of equations). Physiologically this represents no additional contribution of a specific tissue reservoir for CO_2 within the time frame of apnea.

To characterise the O_2-dissociation curve we used a modified form of the equation of Severinghaus [51]. We re-expressed the equation with respect to the partial pressure at 50% (P_{50}) and at 90% (P_{90}) saturation:

$$S_{O_2} = 100[k_2(P_{O_2}{}^3 + k_1 P_{O_2})^{-1} + 1]^{-1} \quad (7)$$

where $k_1 = (9P_{50}{}^3 - P_{90}{}^3)/(P_{90} - 9P_{50})$ and $k_2 = P_{50}{}^3 + k_1 P_{50}$. Values for P_{50} (24.0 mmHg) and P_{90} (53.6 mmHg), were obtained from the data of Delivoria-Papadopoulos [22] for a 9–10 wk-old preterm infant. O_2 content (C_{O_2}, ml ml^{-1}) includes that bound to hemoglobin (Hb, g ml^{-1}) and that dissolved in plasma:

$$C_{O_2} = 1.36\ Hb(S_{O_2}/100) + 0.00003 P_{O_2} \quad (8)$$

The relationship between CO_2 content (C_{CO_2}) and P_{CO_2} was assumed linear:

$$C_{CO_2} = \beta b_{CO_2} P_{CO_2} + k_{CO_2} \quad (9)$$

where $\beta b_{CO_2} = 0.0048$ ml $ml^{-1} mmHg^{-1}$ and $k_{CO_2} = 0.364$ ml ml^{-1} as adapted for STPD from Grodins et al. [52].

Simulations were performed using software written in MATLAB (The Mathworks; Natick, MA).

Theory

A general equation. In an earlier study we developed a general relationship that describes the factors influencing the magnitude of $\dot{S}a_{O_2}$ at any instant in time during apnea [12]:

$$\dot{S}a_{O_2} = \frac{\beta b_{O_2} P_0 \dot{Q}_T}{V_L}(Sa_{O_2} - S\bar{v}_{O_2}) \quad (10)$$

where βb_{O_2} is the capacitance co-efficient of blood for O_2. To specifically demonstrate the role of gas exchange, it is more useful to represent $\dot{S}a_{O_2}$ in terms of $\dot{V}p_{O_2}$. Using Equation 1 for O_2 under conditions of apnea ($\dot{V}_I, \dot{V}_E = 0$), assuming $P_{A_{O_2}} = Pa_{O_2}$, and

using $\dot{S}a_{O_2} = \beta Hb_{O_2}\dot{P}A_{O_2}$, reveals:

$$\dot{S}a_{O_2} = \frac{\beta Hb_{O_2}P_0}{V_L}\dot{V}p_{O_2} \quad (11)$$

where βHb_{O_2} (% $mmHg^{-1}$) is defined as the slope of the O_2-dissociation curve, specifically regarding end-capillary P_{O_2} with respect to S_{O_2}. It is clear from Equation 11 that $\dot{S}a_{O_2}$ is directly proportional to the product $\beta Hb_{O_2} \times \dot{V}p_{O_2}$, which both vary substantially during apneic arterial desaturation. Although Equations 10 and 11 are useful conceptually, values for $(Sa_{O_2} - S\bar{v}_{O_2})$ or $\dot{V}p_{O_2}$ throughout apnea are unknown, and thus $\dot{S}a_{O_2}$ is not simple to predict explicitly.

Special cases. The original framework to understand factors influencing $\dot{S}a_{O_2}$ was based on the assumption that $\dot{V}p_{O_2} = \dot{V}_{O_2}$ [10,23] which does not hold true during apnea [11,12]. However, such an assumption is valid prior to any substantial fall in Sa_{O_2}, and as therefore useful to explicitly describe $\dot{S}a_{O_2}$ immediately upon apnea onset ($\dot{S}a_{O_2}^{onset}$):

$$\dot{S}a_{O_2}^{onset} = \frac{\beta Hb_{O_2}P_0}{V_L}\dot{V}_{O_2} \quad (12)$$

Notably, Equation 12 demonstrates that for any level of $\dot{V}_{O_2}$ and V_L, $\dot{S}a_{O_2}^{onset}$ is intimately related to βHb_{O_2}. Consequently, $\dot{S}a_{O_2}^{onset}$ increases dramatically with reduced resting $P_{A_{O_2}}$ (Figure 11).

Although no simple expression could be written to describe $\dot{S}a_{O_2}$ explicitly for stage 1, we derived an expression for $\dot{S}a_{O_2}$ during stage 2 (see Methods – Derivation of equations), given by:

$$\dot{S}a_{O_2}^{stage\ 2} = \frac{\dot{V}_{O_2}}{1.36\ Hb\ Qb + \dfrac{V_L}{\beta Hb_{O_2}P_0}} \quad (13)$$

Since the total blood O_2 capacity (1.36 Hb Qb) is much greater than $V_L/(\beta Hb_{O_2}P_0)$, $\dot{S}a_{O_2}^{stage\ 2}$ is determined principally by (1.36 Hb Qb) with negligible influence coming from lung volume (V_L) and the slope of the O_2-dissociation curve (βHb_{O_2}), as well as $\dot{Q}T$. Using the values for the preterm infant in Table 2 and maximum $\beta Hb_{O_2} = 2.8\%\ mmHg^{-1}$, Equation 13 predicts that $\dot{S}a_{O_2}^{stage\ 2} = 1.8\%\ s^{-1}$. The little remaining $\dot{V}p_{O_2}$ during stage 2 can be found by combining Equations 11 and 13:

$$\dot{V}p_{O_2} = \frac{V_L/(\beta Hb_{O_2}P_0)}{1.36\ Hb\ Qb + VL/(\beta Hb_{O_2}P_0)}\dot{V}_{O_2} \quad (14)$$

Equation 14 predicts that $\dot{V}p_{O_2} = 8.5\%$ of its resting value during stage 2. Notably, $\dot{V}p_{O_2}$ is increased by reducing Hb and Qb; the greater $\dot{V}p_{O_2}$ and thus a greater rate of alveolar O_2 depletion with reduced blood O_2 capacity (1.36 Hb Qb) will increase $\dot{S}a_{O_2}^{stage\ 2}$.

How can we reconcile that Equation 13 shows that V_L no longer influences $\dot{S}a_{O_2}$ during stage 2, when the general equation (Equation 11) implies that reduced V_L will accelerate $\dot{S}a_{O_2}$ throughout apneic desaturation? Equation 14 reveals that during stage 2, elevated V_L also acts to increase $\dot{V}p_{O_2}$; thus nearly entirely offsetting the direct influence on $\dot{S}a_{O_2}$. The same applies for reduced βHb_{O_2}, which acts to elevate $\dot{V}p_{O_2}$ and therefore no longer accelerates $\dot{S}a_{O_2}$ during stage 2.

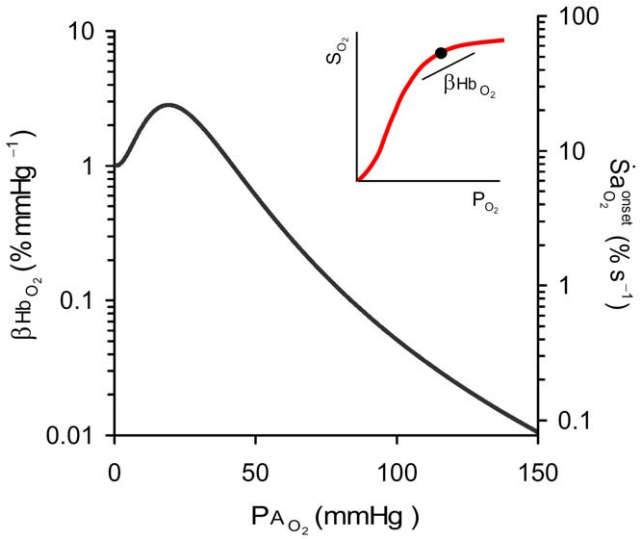

Figure 11. Relationship between the slope of the oxy-hemoglobin dissociation curve and alveolar P_{O_2}. Note that reduced alveolar P_{O_2} ($P_{A_{O_2}}$) causes a substantial increase in the slope of the oxy-hemoglobin dissociation curve (βHb_{O_2}; see inset) and in $\dot{S}a_{O_2}$ at apnea onset ($\dot{S}a_{O_2}^{onset}$; based on Equation 12).
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Derivation of equations

Here we derive the explicit equations used within the current study to encapsulate key relationships pertaining to gas exchange and arterial desaturation during apnea.

Stage 2 arterial O_2 desaturation.. This section details the derivation of an explicit equation to predict the rate of both arterial and venous desaturation during the severe desaturation of stage 2, a phase where $\dot{V}p_{O_2}$ is substantially reduced below $\dot{V}_{O_2}$ and both Sa_{O_2} and $S\bar{v}_{O_2}$ fall at the same rate. Ignoring dissolved plasma O_2, consideration of Equation 1 for O_2 and assuming $\dot{S}a_{O_2} = \dot{S}\bar{v}_{O_2}$ yields:

$$\dot{S}a_{O_2} = \frac{\dot{V}_{O_2} - 1.36\ Hb\ \dot{Q}T(Sa_{O_2}(t-T_a) - S\bar{v}_{O_2})}{1.36\ Hb\ Qv} \quad (15)$$

By substituting the following relationships into Equation 15: $(Sa_{O_2}(t\text{-}T_a)\text{-}S\bar{v}_{O_2}) = (Sa_{O_2}\text{-}S\bar{v}_{O_2}) + \dot{S}a_{O_2}T_a$; $T_a = Qa/\dot{Q}T$; $Qb = Qa+Qv$; $\dot{V}p_{O_2} = 1.36\ Hb\ \dot{Q}T(Sa_{O_2}\text{-}S\bar{v}_{O_2})$; it can be shown that $\dot{S}a_{O_2}$ is directly proportional to the difference between $\dot{V}_{O_2}$ and $\dot{V}p_{O_2}$, where:

$$\dot{S}a_{O_2} = \frac{\dot{V}_{O_2} - \dot{V}p_{O_2}}{1.36\ Hb\ Qb} \quad (16)$$

Combining Equations 11 and 16 yields Equation 13.

Estimation of effective blood volume for CO_2. Using the same methodology as described above, the ratio of $\dot{C}\bar{v}_{O_2}$ to $\dot{C}\bar{v}_{CO_2}$ during stage 2 can be used to estimate the ratio of Qb_{CO_2} to Qb_{O_2}. $\dot{C}\bar{v}_{O_2}$ and $\dot{C}\bar{v}_{CO_2}$ can be found using:

$$\dot{C}a_G = \dot{C}\bar{v}_G = -\frac{\dot{V}_G}{Qb_G + \dfrac{V_L}{\beta b_G P_0}} \quad (17)$$

where Qb_{O_2} and Qb_{CO_2} are the effective blood volumes for O_2/

CO_2; βb_{CO_2} is the capacitance coefficient for CO_2. Neglecting pulmonary gas exchange, combining Equation 17 for O_2 and CO_2 gives:

$$\frac{Qb_{CO_2}}{Qb_{O_2}} = -\frac{\dot{C}\bar{v}_{O_2}}{\dot{C}\bar{v}_{CO_2}}\frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}} \tag{18}$$

Equation 18 permitted the calculation of Qv_{CO_2}/Qv_{O_2} based on published data [53; their Figure 3] where during apnea the rate of rise in $C\bar{v}_{CO_2}$ is very close to the rate of fall in the product of $C\bar{v}_{O_2}$ and the respiratory exchange ratio (RER); using $-\dot{C}\bar{v}_{O_2}/\dot{C}\bar{v}_{CO_2} = 1.29$ from their data, and assuming resting RER = 0.8, we find that $Qb_{CO_2}/Qb_{O_2} = 1.03$ or approximately 1. Thus Qv_{CO_2}/Qv_{O_2} is assumed to be 1.

Stage 1 hypercapnia. Here we develop a relationship to describe the time-course of alveolar/arterial hypercapnia during stage 1 for CO_2. Using Equation 1 for CO_2, taking $\dot{V}_I, \dot{V}_E = 0$, gives the relationship $\dot{P}_{A_{CO_2}} = P_0\dot{V}p_{CO_2}/V_L$. Substituting the steady-state Fick equation, $\dot{V}p_{CO_2} = \beta b_{CO_2}\dot{Q}_T(Pa_{CO_2} - P\bar{v}_{CO_2})$, assuming alveolar-arterial equilibrium ($Pa_{CO_2} = P_{A_{CO_2}}$), using $\dot{V}p_{CO_2} = \dot{V}_{CO_2}$ under resting conditions, assuming that $P\bar{v}_{CO_2}$ is constant, and solving for $P_{A_{CO_2}}$ yields:

$$P_{A_{CO_2}} = P\bar{v}_{CO_2} - \frac{\dot{V}_{CO_2}}{\beta b_{CO_2}\dot{Q}_T}e^{-\frac{\beta b_{CO_2}P_0\dot{Q}_T}{V_L}t} \tag{19}$$

Calculating the rate of rise in $P_{A_{CO_2}}$ ($\dot{P}_{A_{CO_2}}$) by taking the derivative gives:

$$\dot{P}_{A_{CO_2}} = \frac{P_0\dot{V}_{CO_2}}{V_L}e^{-\frac{\beta b_{CO_2}P_0\dot{Q}_T}{V_L}t} \tag{20}$$

Equations 19 and 20 describe the slowing of $\dot{P}_{A_{CO_2}}$ from the initial rate $\dot{P}_{A_{CO_2}} = P_0\dot{V}p_{CO_2}/V_L$ as $P_{A_{CO_2}}$ rises towards $P\bar{v}_{CO_2}$. Specifically, the time constant $\tau = V_L/(\beta b_{CO_2}P_0\dot{Q}_T)$ demonstrates that high βb_{CO_2} causes a rapid slowing of $\dot{V}p_{CO_2}$ and hence of $\dot{P}_{A_{CO_2}}$ as the arterial value approaches venous value. Indeed, fitting an exponential curve to the $P_{A_{CO_2}}$ trace (Figure 2) during the first 5 s of apnea yielded a rapid time constant of 1.26 s, a value close to that predicted by $VL/(\beta b_{CO_2}P_0\dot{Q}_T)$. The corollary is that the low value of βb_{O_2} prevents the slowing of $\dot{V}p_{O_2}$ as desaturation progresses, giving rise to a rapid $P_{A_{O_2}}$ decline and thus rapid arterial desaturation. Likewise, further reducing βb_{O_2} by lowering hemoglobin content potentiates such effect.

Impact of supplemental O_2. The delay (right-shift) in arterial desaturation during apnea with increasing supplemental O_2 (ΔPI_{O_2}) can be predicted explicitly. Using Equation 1 for O_2 under the conditions of apnea, and assuming $\Delta P_{I_{O_2}} = \Delta P_{A_{O_2}}$, the delay ($\Delta t$) in arterial desaturation is given by:

$$\Delta t = \frac{\Delta PI_{O_2}V_L}{P0\dot{V}_{O_2}} \tag{21}$$

Author Contributions

Conceived and designed the experiments: SAS PJB. Performed the experiments: SAS. Analyzed the data: SAS BAE MRD MHW PJB. Wrote the paper: SAS BAE VJK MRD MHW PJB. Designed and implemented the model: SAS VJK MRD MHW.

References

1. Barrington K, Finer N (1991) The natural history of the appearance of apnea of prematurity. Pediatr Res 29: 372–375.
2. Poets CF, Stebbens VA, Samuels MP, Southall DP (1993) The relationship between bradycardia, apnea, and hypoxemia in preterm infants. Pediatr Res 34: 144–147.
3. Perlman JM, Volpe JJ (1985) Episodes of apnea and bradycardia in the preterm newborn: impact on cerebral circulation. Pediatrics 76: 333–338.
4. Janvier A, Khairy M, Kokkotis A, Cormier C, Messmer D, et al. (2004) Apnea is associated with neurodevelopmental impairment in very low birth weight infants. J Perinatol 24: 763–768.
5. Prabhakar NR, Peng YJ, Kumar GK, Pawar A (2007) Altered carotid body function by intermittent hypoxia in neonates and adults: relevance to recurrent apneas. Respir Physiol Neurobiol 157: 148–153.
6. Row BW, Kheirandish L, Neville JJ, Gozal D (2002) Impaired spatial learning and hyperactivity in developing rats exposed to intermittent hypoxia. Pediatr Res 52: 449–453.
7. Kato I, Groswasser J, Franco P, Scaillet S, Kelmanson I, et al. (2001) Developmental characteristics of apnea in infants who succumb to sudden infant death syndrome. Am J Respir Crit Care Med 164: 1464–1469.
8. Naeye RL (1974) Hypoxemia and the sudden infant death syndrome. Science 186: 837–838.
9. Poets CF, Southall DP (1991) Patterns of oxygenation during periodic breathing in preterm infants. Early Hum Dev 26: 1–12.
10. Fletcher EC, Goodnight S, Miller T, Luckett RA, Rosborough J, et al. (1990) Atelectasis affects the rate of arterial desaturation during obstructive apnea. J Appl Physiol 69: 1863–1868.
11. Lanphier EH, Rahn H (1963) Alveolar gas exchange during breath holding with air. J Appl Physiol 18: 478–482.
12. Wilkinson MH, Berger PJ, Blanch N, Brodecky V (1995) Effect of venous oxygenation on arterial desaturation rate during repetitive apneas in lambs. Respir Physiol 101: 321–331.
13. Farmery AD, Roe PG (1996) A model to describe the rate of oxyhaemoglobin desaturation during apnoea. Br J Anaesth 76: 284–291.
14. Poets CF (2004) Apparent life-threatening events and sudden infant death on a monitor. Paediatr Respir Rev 5 Suppl A: S383–386.
15. Poets CF, Rau GA, Neuber K, Gappa M, Seidenberg J (1997) Determinants of lung volume in spontaneously breathing preterm infants. Am J Respir Crit Care Med 155: 649–653.
16. Henderson-Smart DJ (1980) Vulnerability to hypoxemia in the newborn. Sleep 3: 331–342.
17. Strohl KP, Altose MD (1984) Oxygen saturation during breath-holding and during apneas in sleep. Chest 85: 181–186.
18. Finer NN, Higgins R, Kattwinkel J, Martin RJ (2006) Summary proceedings from the apnea-of-prematurity group. Pediatrics 117: S47–51.
19. Upton CJ, Milner AD, Stokes GM (1991) Apnoea, bradycardia, and oxygen saturation in preterm infants. Arch Dis Child 66: 381–385.
20. Adams JA, Zabaleta IA, Sackner MA (1997) Hypoxemic events in spontaneously breathing premature infants: etiologic basis. Pediatr Res 42: 463–471.
21. Stewart IB, Bulmer AC, Sharman JE, Ridgway L (2005) Arterial oxygen desaturation kinetics during apnea. Med Sci Sports Exerc 37: 1871–1876.
22. Delivoria-Papadopoulos M, Roncevic NP, Oski FA (1971) Postnatal changes in oxygen transport of term, preterm, and sick infants: The role of red cell 2,3-Diphosphoglycerate and adult hemoglobin. Pediatric Research 5: 235–245.
23. Fletcher EC, White SG, Munafo D, Miller CC, 3rd, Luckett R, et al. (1991) Effect of cardiac output reduction on rate of desaturation in obstructive apnea. Chest 99: 452–456.
24. Stark AR, Cohlan BA, Waggener TB, Frantz ID, 3rd, Kosch PC (1987) Regulation of end-expiratory lung volume during sleep in premature infants. J Appl Physiol 62: 1117–1123.
25. Cartlidge PH, Rutter N (1987) Percutaneous respiration in the newborn infant. Effect of gestation and altered ambient oxygen concentration. Biol Neonate 52: 301–306.
26. Cartlidge PH, Rutter N (1988) Percutaneous respiration in the new-born infant. Effect of ambient oxygen concentration on pulmonary oxygen uptake. Biol Neonate 54: 68–72.
27. Reix P, Arsenault J, Dome V, Fortier PH, Lafond JR, et al. (2003) Active glottal closure during central apneas limits oxygen desaturation in premature lambs. J Appl Physiol 94: 1949–1954.
28. Poets CF (2003) Pathophysiology of apnea of prematurity. Implications from observational studies. In: Oommen MP, ed. Respiratory control and disorders in the newborn. New York: Marcel Dekker Inc. pp 295–316.

29. Edwards BA, Sands SA, Feeney C, Skuza EM, Brodecky V, et al. (2009) Continuous positive airway pressure reduces loop gain and resolves periodic central apneas in the lamb. Respir Physiol Neurobiol;doi:10.1016/j.resp.2009.07.006.
30. Westkamp E, Soditt V, Adrian S, Bohnhorst B, Groneck P, et al. (2002) Blood transfusion in anemic infants with apnea of prematurity. Biol Neonate 82: 228–232.
31. Hjalmarson O, Sandberg K (2002) Abnormal lung function in healthy preterm infants. Am J Respir Crit Care Med 165: 83–87.
32. Olhager E, Forsum E (2003) Total energy expenditure, body composition and weight gain in moderately preterm and full-term infants at term postconceptional age. Acta Paediatr 92: 1327–1334.
33. Tourneux P, Leke A, Kongolo G, Cardot V, Degrugilliers L, et al. (2008) Relationship between functional residual capacity and oxygen desaturation during short central apneic events during sleep in "late preterm" infants. Pediatr Res 64: 171–176.
34. Sekar KC, Duke JC (1991) Sleep apnea and hypoxemia in recently weaned premature infants with and without bronchopulmonary dysplasia. Pediatr Pulmonol 10: 112–116.
35. Weinstein MR, Oh W (1981) Oxygen consumption in infants with bronchopulmonary dysplasia. J Pediatr 99: 958–961.
36. Hjalmarson O, Sandberg KL (2005) Lung function at term reflects severity of bronchopulmonary dysplasia. J Pediatr 146: 86–90.
37. Kaempf JW, Campbell B, Brown A, Bowers K, Gallegos R, et al. (2007) PCO2 and room air saturation values in premature infants at risk for bronchopulmonary dysplasia. J Perinatol.
38. Dechert R, Wesley J, Schafer L, LaMond S, Beck T, et al. (1985) Comparison of oxygen consumption, carbon dioxide production, and resting energy expenditure in premature and full-term infants. J Pediatr Surg 20: 792–798.
39. Hey EN (1969) The relation between environmental temperature and oxygen consumption in the new-born baby. J Physiol 200: 589–603.
40. Bauer J, Maier K, Linderkamp O, Hentschel R (2001) Effect of caffeine on oxygen consumption and metabolic rate in very low birth weight infants with idiopathic apnea. Pediatrics 107: 660–663.
41. Bucher HU, Duc G (1988) Does caffeine prevent hypoxaemic episodes in premature infants? A randomized controlled trial. Eur J Pediatr 147: 288–291.
42. McEvoy C, Mendoza ME, Bowling S, Hewlett V, Sardesai S, et al. (1997) Prone positioning decreases episodes of hypoxemia in extremely low birth weight infants (1000 grams or less) with chronic lung disease. J Pediatr 130: 305–309.
43. Kassim Z, Donaldson N, Khetriwal B, Rao H, Sylvester K, et al. (2007) Sleeping position, oxygen saturation and lung volume in convalescent, prematurely born infants. Arch Dis Child Fetal Neonatal Ed 92: F347–350.
44. Wagaman MJ, Shutack JG, Moomjian AS, Schwartz JG, Shaffer TH, et al. (1979) Improved oxygenation and lung compliance with prone positioning of neonates. J Pediatr 94: 787–791.
45. Hill JR, Rahimtulla KA (1965) Heat balance and the metabolic rate of new-born babies in relation to environmental temperature; and the effect of age and of weight on basal metabolic rate. J Physiol 180: 239–265.
46. Blair PS, Sidebotham P, Berry PJ, Evans M, Fleming PJ (2006) Major epidemiological changes in sudden infant death syndrome: a 20-year population-based study in the UK. Lancet 367: 314–319.
47. Poets CF, Samuels MP, Wardrop CA, Picton-Jones E, Southall DP (1992) Reduced haemoglobin levels in infants presenting with apparent life-threatening events–a retrospective investigation. Acta Paediatr 81: 319–321.
48. Grodins FS, Buell J, Bart AJ (1967) Mathematical analysis and digital simulation of the respiratory control system. J Appl Physiol 22: 260–276.
49. Milner AD, Greenough A (2004) The role of the upper airway in neonatal apnoea. Semin Neonatol 9: 213–219.
50. Guyton AC (1976) The systemic circulation. Textbook of medical physiology. 5 ed. Philapelphia: W. B. Saunders Company. pp 237–249.
51. Severinghaus JW (1979) Simple, accurate equations for human blood O2 dissociation computations. J Appl Physiol 46: 599–602.
52. Grodins FS, Gray JS, Schroeder KR, Norins AL, Jones RW (1954) Respiratory responses to CO2 inhalation; a theoretical study of a nonlinear biological regulator. J Appl Physiol 7: 283–308.
53. Hong SK, Lin YC, Lally DA, Yim BJ, Kominami N, et al. (1971) Alveolar gas exchanges and cardiovascular functions during breath holding with air. J Appl Physiol 30: 540–547.
54. Hulskamp G, Hoo AF, Ljungberg H, Lum S, Pillow JJ, et al. (2003) Progressive decline in plethysmographic lung volumes in infants: physiology or technology? Am J Respir Crit Care Med 168: 1003–1009.
55. Hill JR, Robinson DC (1968) Oxygen consumption in normally grown, small-for-dates and large-for-dates new-born infants. J Physiol 199: 685–703.
56. Walther FJ, Siassi B, Ramadan NA, Ananda AK, Wu PY (1985) Pulsed Doppler determinations of cardiac output in neonates: normal standards for clinical use. Pediatrics 76: 829–833.
57. Linderkamp O, Versmold HT, Riegel KP, Betke K (1977) Estimation and prediction of blood volume in infants and children. Eur J Pediatr 125: 227–234.
58. Koch G (1968) Alveolar ventilation, diffusing capacity and the A-a PO2 difference in the newborn infant. Respir Physiol 4: 168–192.